The views expressed in this paper are those of the author and do not necessarily reflect the views of the Department of Defense or any of its agencies. This document may not be released for open publication until it has been cleared by the appropriate military service or government agency.

STRATEGY RESEARCH PROJECT

ADENOVIRUS VACCINE SHORTFALL: IMPACT ON READINESS AND DEPLOYABILITY

BY

COLONEL NIRANJAN BALLIRAM United States Army

DISTRIBUTION STATEMENT A:

Approved for Public Release.
Distribution is Unlimited.

USAWC CLASS OF 2002



U.S. ARMY WAR COLLEGE, CARLISLE BARRACKS, PA 17013-5050

20020604 256

USAWC STRATEGY RESEARCH PROJECT

ADENOVIRUS VACCINE SHORTFALL: IMPACT ON READINESS AND DEPLOYABILITY

by

Colonel Niranjan Balliram United States Army

Colonel Cloyd Gatrell
Project Advisor

The views expressed in this academic research paper are those of the author and do not necessarily reflect the official policy or position of the U.S. Government, the Department of Defense, or any of its agencies.

U.S. Army War College CARLISLE BARRACKS, PENNSYLVANIA 17013

<u>DISTRIBUTION STATEMENT A</u>: Approved for public release. Distribution is unlimited.

ABSTRACT

AUTHOR:

Colonel Niranjan Balliram

TITLE:

Adenovirus Shortfall: Its Impact on Readiness and Deployability

FORMAT:

Strategy Research Project

DATE:

13 December 2001

PAGES: 30

CLASSIFICATION: Unclassified

Vaccines enhance our national defense by protecting the health of men and women who serve their nation in uniform. In 1995, Wyeth Laboratories, the sole licensed manufacturer of the adenovirus vaccines, ceased production for economic reasons. Department of Defense was forewarned of Wyeth's problems in meeting the military's need for these vaccines, but in 1984 the Pentagon denied a request from Wyeth for five million dollars to upgrade its facility to meet regulatory standards. That decision resulted in the complete loss of adenovirus vaccine production. This paper assesses the impact of the shortfall of the adenovirus vaccine on training, readiness, deployability, and the military health care system; and examines the cost of procuring a new manufacturer for the vaccine.

TABLE OF CONTENTS

ABSTRACTIII
ADENOVIRUS SHORTFALL: ITS IMPACT ON READINESS AND DEPLOYABILITY1
BACKGROUND1
VIRUS IDENTIFICATION2
VACCINE DEVELOPMENT4
REVIEW OF IMMUNIZATION POLICY6
VACCINE SHORTFALL6
VACCINE PROCUREMENT ISSUES8
EMERGENCE OF AN OLD NEMESIS9
COST BENEFIT ANALYSIS11
IMPACT ON READINESS AND DEPLOYABILITY12
IMPACT ON HEALTH CARE SYSTEM13
IMPACT OF PROCURING A NEW MANUFACTURER14
CONCLUSION15
ENDNOTES17
3IBLIOGRAPHY21

ADENOVIRUS VACCINE SHORTFALL: IMPACT ON READINESS AND DEPLOYABILITY

The preservation of the soldier's health should be the commandant's first and greatest care...

- Regulations for the Order and Discipline of Troops, Congress, 1779

Vaccines enhance our national defense by protecting the health of the men and women who serve their nation in uniform. Since 1971, the Department of Defense (DOD) has directed that adenovirus vaccines types four and seven be given to military recruits in basic combat training to prevent febrile respiratory disease outbreaks and person-to-person transmission of these specific adenovirus types.¹

The adenovirus types 4 and 7 vaccines are used only by the military. These adenovirus vaccines are safe and effective and reduced acute respiratory disease (ARD) morbidity in basic training populations by 50%-90% since the 1970's. This reduced hospitalizations, recycling of basic trainees, and disruption of basic training cycles, thereby increasing military readiness.²

In 1995, Wyeth Laboratories, the sole licensed manufacturer of these vaccines, ceased production for economic reasons.³ DOD was forewarned of Wyeth's problems in meeting the military's need for these vaccines. In 1984 the Pentagon denied a request from Wyeth for five million dollars to upgrade its facility to meet regulatory standards.⁴ That decision resulted in the complete loss of the adenovirus vaccine. This paper assesses the impact of the shortfall of the adenovirus vaccine on training, readiness, deployability, and the military health care system; and examines the cost of procuring a new manufacturer for the vaccine.

BACKGROUND

Prior to the adenovirus vaccine program implemented in 1971, the leading cause of morbidity and hospitalization among basic trainees was acute respiratory disease due to adenovirus types four and seven.⁵ Disease outbreaks followed recurrent patterns; basic training commanders could predict when the ARD epidemic would occur in their training cycles. Adenovirus outbreaks usually occurred during the third week of basic combat training. At northern Basic Combat Training posts with a cohort of 10,000 recruits, as many as 600-800 trainees were hospitalized per week during fall and winter peaks of the disease.⁶

Epidemiological studies of civilian college and university students, university employees and selected hospital cases of acute respiratory illnesses show that this adenovirus disease occurs in the civilian population, but does not require hospitalization. Only 0.3% of the civilian population exposed to the adenovirus develop clinical symptoms, ranging from minor respiratory

illnesses to pneumonia.⁸ In contrast, the adenovirus types 4 and 7 which occur primarily in military recruits and usually peak three to six weeks after onset of training pose a unique problem for the military's nine basic training centers.⁹ Predisposing conditions place trainees at risk to be infected with the virus: living in cramped quarters, close contact with each other, stress of basic training and exposure to pathogens in disease endemic areas.¹⁰

Medical personnel developed specific criteria for admitting basic trainees to military hospitals. Trainees who had a temperature above 100 degrees Fahrenheit were usually admitted for treatment for symptoms and rest; observation and screening for other serious illnesses, such as meningitis; and to prevent the spread of the disease among the other healthy trainees.¹¹

VIRUS IDENTIFICATION

In their research studying the growth of human adenoid tissue in roller tube culture during the winter and spring months of 1953, Rowe and associates discovered that some of the adenoids removed from children (Children's Hospital Washington D.C, Naval Hospital, Bethesda, MD) exhibited a new type of cytopathogenic agent which they named "adenoid degeneration agent." They found that the incubation period of the cytopathogenic agent on human epithelium was usually 4 to 8 days, but with higher dilution of the inoculum, could be as long as 23 days. ¹³

About the same time during the winter of 1953, there was an ARD outbreak among basic trainees at Fort Leonard Wood, Missouri. Independently, Hilleman and Werner from the Walter Reed Institute of Research (WRAIR) isolated a microbial agent which they named "respiratory illness agent (RI-67 virus)" from the throat washings of a patient with atypical pneumonia. They found that this patient and others in the epidemic who were diagnosed with atypical pneumonia (ATP) or with undifferentiated acute respiratory disease (ARD) had specific neutralizing and complement-fixing antibodies for RI-67.¹⁴

Further laboratory tests conducted by both Hilleman and Rowe showed that the adenoid degenerative agent and the respiratory illness agents had an "immunological relationship" and led to the same clinical syndrome (ARD, pharyngitis, conjunctivitis, pneumonitis and atypical pneumonia).¹⁵ These agents were then categorized as adenovirus.¹⁶ The discovery of the adenovirus was most significant because it led to the development of vaccines to control its spread among basic combat trainees.

In 1960, the Armed Forces Commission on Acute Respiratory Diseases concluded that adenovirus was the main cause of Acute Respiratory Disease in military recruits. Outbreaks of

ARD at military training bases were thereafter attributed to adenoviruses.¹⁷ Fever, malaise, nasal congestion, sore throat, hoarseness, headaches and coughing characterize adenoviral acute respiratory disease. During the 1960s ARD due to adenoviruses types four and seven infected over 80% of basic trainees; approximately 20% were hospitalized (5-8/100 soldiers per week).¹⁸ About 10% of the basic trainees who went to sick call with ARD symptoms had pneumonitis on X-ray, and 20% of those trainees who were diagnosed with primary atypical pneumonia (PAP) had an infection due to adenovirus.¹⁹ Although fatal adenovirus pneumonia occurs mostly in children, there were three Army basic trainee fatalities from pneumonias associated with adenovirus type 7 at Fort Leonard Wood, Missouri, between March and July 1970; none of the three recruits had received adenovirus type 7 vaccine, which at that time was still undergoing limited clinical trial.²⁰

During a 1965 eight-week winter basic training cycle at Fort Dix, New Jersey, a field team from WRAIR studied the impact of ARD due to adenovirus on a platoon of 48 basic combat trainees. ²¹Throughout the training cycle the combat trainees were monitored daily to detect any signs and symptoms of respiratory tract infections. There were 92 episodes of respiratory illness noted. Among those, 24 basic trainees were hospitalized with severe febrile illness. The disease showed a definite pattern: the incidence rose during the first two weeks of training and peaked during the second and third weeks. During the second and third week peak of the disease combat trainees experienced severe febrile ARD; it was during this time period that most of them were hospitalized. Of the 24 combat trainees hospitalized with the severe febrile ARD, 18 had adenovirus type 4. Another 19 combat trainees had a less severe form of febrile ARD adenovirus type 4 that did not require hospitalization. Nine of the trainees from this platoon who were ill were recycled to other companies because they could not keep pace with their peers in the training cycle. ²²

The experience documented in this study at Fort Dix is typical of the effects of ARD on basic combat trainees at other basic combat training posts during the winter months. During an 8-week training cycle more than 50% of the trainees in a unit may be hospitalized with febrile ARD due to adenovirus infections, primarily during the first two or three weeks of training. At Fort Dix this outbreak severely impacted the military health care system: the hospital dedicated four wards and an additional four wards from the hospital annex to care for patients during the ARD season.²³ Hospitals at other basic training sites adopted similar procedures.

Acute respiratory disease outbreaks interrupted other basic training programs. Several soldiers from each company were recycled each rotation due to hospitalization; sometimes entire training platoons were recycled. Commanders repeatedly had to modify their programs of

instruction to accommodate the recycling of trainees. The very high economic impact due to the cost of hospitalization and recycling of trainees will be discussed later under cost analysis. Shortly after the 1965 ARD outbreak at Fort Dix the Army acknowledged the need for an adenovirus vaccination program.

Training center cadre implemented some environment changes to reduce the spread of ARD infection among their training units. These included segregating small units, and alternating sleeping arrangements (head to toe).²⁴ Head to toe sleeping assumes that transfer of respiratory infections occurs in the barracks. This measure is difficult to enforce and consists of sleeping basic combat trainees in a line of bunks alternating head and foot positions to increase the breathing distance between trainees. Army Regulation 415-50 requires 72 square feet of net floor space (bed and locker) per basic combat trainee; that standard was intended to reduce the spread of infectious agents based on the influenza attack rates in troops living in barracks in World War 1.²⁵ Theoretically, combat trainees spend a significant amount of time sleeping. Air exchange ratios in barracks are often inadequate given the close quarters and distance between breathing zones. Even if the 72 square feet requirement is complied with in the barracks it is difficult to maintain in the classrooms.

VACCINE DEVELOPMENT

Adenovirus vaccine research started in the 1950s. During the first six years of developing and testing these vaccines there were several successes but also setbacks due to oncogenicity, problems associated with monovalent immunization and virus stability.²⁶

In 1956, Hilleman and his associates from WRAIR used two strains to develop a respiratory illness (RI) vaccine: adenovirus type 4 virus (RI-67 originally recovered from human tracheal epithelium tissue culture throat washing of a case of atypical pneumonia) and adenovirus type 7 virus (RI-4–202 recovered in human amniotic epithelium tissue culture from a throat washing from a case of ARD). They tested the vaccine on 12 volunteers at WRAIR; almost all of the volunteers developed an increased amount of neutralizing antibody against adenovirus type 4 and adenovirus type 7 and also adenovirus type 3 virus. ²⁷

In February and March 1956, field trials of the RI vaccine were conducted at Fort Dix, because data showed that RI infection rates were consistently high at this training post during the winter months.²⁸ The researchers divided the trainees into two groups, 311 received RI vaccinations and 313 in the control group received placebo. Results showed there was a significant decline in hospitalizations during the second, third and fourth weeks post RI vaccination, the period typically associated with high incidence of RI disease among basic

trainee.²⁹Only 6 of the 311 combat trainees who received the RI vaccine were hospitalized, compared to 64 of 313 combat trainees who received the placebo inoculations.³⁰ The conclusion of this initial field trial was that the RI formalin-killed vaccine was highly effective against acute respiratory diseases caused by viruses of the RI (adenovirus) family.³¹

In 1963, field trials of inactivated adenovirus vaccines showed that certain of the human adenovirus types (3,7,14, and 21) were contaminated with the oncogenic virus SV-40 and had the potential to cause malignant transformation of rat cells; concerns over this potential to cause cancer resulted in cancellation of the vaccination program.³²

Concurrently, Chanock and his associates at the National Institutes of Allergy and Infectious Diseases developed an effective live oral enteric-coated vaccine against adenovirus type 4 infections.³³ In 1964 at Parris Island, Dr. Chanock and Navy physicians successfully demonstrated that the adenovirus type 4 vaccine effectively reduced hospitalizations due to ARD caused by adenovirus type 4 infections. In 1965 the Army conducted a successful pilot trial with this adenovirus type 4 vaccine among six companies of basic combat trainees at Fort Dix, New Jersey: there was a 95% reduction of hospitalizations associated with ARD due to adenovirus type 4 infections. In January 1967, the Army implemented the adenovirus type 4 vaccine program at all basic training posts.³⁴ However, 1967 data from the Army Surveillance program showed that the adenovirus type 4 vaccine was not very effective in controlling the acute respiratory disease seen among the basic trainees.³⁵

From 1968 through 1970, researchers at WRAIR developed and tested a live oral adenovirus type 7 vaccine to be used simultaneously with adenovirus type 4 vaccine to control both types of ARD.³⁶ In 1970, the Army administered adenovirus type 4 and adenovirus type 7 vaccines simultaneously at Fort Dix, Fort Leonard Wood and Fort Lewis; this combination proved very effective and significantly reduced ARD infections among basic trainees.³⁷

In 1971, the U.S. military started immunizing all male basic trainees with adenovirus type 4 and type 7 vaccines during the winter months. The goal was not to eradicate the disease but to control it. 38 Since there had been no adenovirus outbreaks among female soldiers and the adenovirus vaccine was a live virus with potential effects on pregnancy, military medical authorities decided not to immunize female soldiers. In 1983 the Army and Navy changed the program to include vaccination of new male trainees throughout the year. This process has continued to the present (Fall 2001). Although there was no adenovirus outbreak at Lackland Air Force Base in the mid-1970's, studies were conducted with simultaneous administration of adenovirus type 4 and type 7 vaccines. In the mid-1980s the Air Force discontinued the routine administration of the adenovirus vaccines, opting instead for a surveillance program for ARD

due to adenoviruses and using the adenovirus vaccine as needed. That remains the current Air Force, practice.³⁹ During the first three years of the combination vaccination program, there was a 36%-73% reduction in ARD infections and a 50% reduction in adenovirus related hospital admissions among all basic combat training posts.⁴⁰

REVIEW OF IMMUNIZATION POLICY

The Advisory Committee on Immunization Practices develops the Immunization recommendation for the nation. In 1984 they stated that there was no need to immunize the civilian population and recommended that the live oral adenovirus vaccines be given only to the military population.⁴¹

In October 1986 the Department of Defense issued a policy stating that the Assistant Secretary of Defense for Health Affairs and the Service Secretaries of the Military Departments, in consultation with the Armed Forces Medical Intelligence Center, Armed Forces Epidemiological Board and the Armed Forces Pest Management Board, shall identify military unique requirements for vaccine research development and production, and develop and implement general principles and specific procedures to be followed in the prophylactic immunization programs of the Armed Forces. Prophylactic immunization includes the use of vaccine, toxoid, or other immunizing agent for the prevention of disease, including the maintenance of immune status by re-immunization.⁴²

In 1995, Army Regulation 40-562, <u>Immunizations and Chemoprophylaxis</u> (revised, original policy issued July 1986) recommended adenovirus vaccines types 4 and 7 be given to all recruits.⁴³

On 13 July 2001, The Surgeon General of the United States Army testified before the Armed Services Subcommittee on Military Personnel. He stated, "Health is not only the absence of disease and disability, it is an optimally fit soldier, prepared mentally, physically, socially and in all other aspects of life to perform the missions assigned. It is a protected soldier not only against the routine endemic diseases for which we have a plethora of vaccines, but the uniquely military challenges such as Adenovirus for which we have a vaccine shortfall because there is no commercial market."

VACCINE SHORTFALL

In July 1980, Wyeth Laboratory became the sole licensed manufacturer of the oral live adenovirus vaccines types 4 and 7. The Pennsylvania plant producing the vaccine was in

severe disrepair. The machines making the vaccine were outdated-one was subsequently donated to the National Museum of American History in Washington. The infectious live adenovirus used in the vaccines was being transported on a gurney without proper safeguards to prevent its accidental release. In 1984, the Food and Drug Administration inspectors instructed Wyeth to upgrade its facilities. Since the market for adenovirus vaccine was limited to the military, Wyeth determined it was not economically prudent to upgrade the facility without help from the Government, and asked the Department of Defense for five million dollars to fund an upgrade.⁴⁵

The Defense Personnel Service Center (DPSC) in Philadelphia which was responsible for the Wyeth contract requested an increase in its budget to fund the project but was turned down by senior leaders at the Pentagon. In 1985 the DPSC sought other manufacturers for this vaccine, but none were interested. Wyeth concluded it was not cost effective to comply with the stringent standards and facility upgrade requirements of the regulating agencies. In the 1994 Wyeth informed Department of Defense that they could not comply with the Food and Drug Administration (FDA), Environmental Protection Agency and OSHA standards, and would have to close the laboratory.⁴⁶

In 1996, Wyeth delivered to DOD its last batch of adenovirus types 4 and 7 vaccines (a year's supply, projected expiration date for adenovirus type 4 was June 1998 and that for type 7 was December 1998); current year-round vaccination policy would deplete supply by June 1997. Shortly thereafter, Wyeth destroyed the vaccine producing facility. Based on real-time potency tests, the FDA extended the 1998 expiration date of those one year. In 1997, in order to conserve vaccine after the closure of Wyeth laboratory adenovirus production line, the Armed Forces Epidemiological Board recommended a change in the vaccination policy at basic training sites from year-round to seasonal. Wyeth informed DPSC in 1998 that due to deterioration of enteric coating on the adenovirus type 4 vaccine, its life could not be extended. However, with the change in vaccination policy, DPSC had projected that their supply of adenovirus type 7 vaccines would be exhausted by February of 1999. Since the change in vaccination policy, there has been a significant rise in ARD infections due to adenovirus types 4 and 7 among basic training populations. Two training centers have experienced respiratory epidemics with adenovirus affecting thousands of trainees and overloading the local healthcare systems. Two Navy recruits developed respiratory infection and died during the summer of 2000.

VACCINE PROCUREMENT ISSUES

From 1984 to 1998 senior infectious disease experts of the Army Medical Department briefed Pentagon leaders about the implications of the loss of this vaccine and its effect on basic training and readiness.

In February 1995, the Armed Forces Epidemiological Board (AFEB) passed the following findings and recommendations to the Assistant Secretary of Defense for Health Affairs:

- 1. The risk and impact of Adenovirus infections to military operations are concerns of highest significance at present and for the foreseeable future.
- 2. Assuring continuing and timely availability of the current vaccine should be given the highest acquisition priority.
- 3. Alternative scenarios for the use of vaccine, such as outbreak control, should be considered and researched to determine the relative efficacy of such programs.
- 4. Long term arrangements to assure a stable and reliable source of vaccine should be pursued vigorously.
- 5. Epidemiological surveillance activities, including diagnostic capabilities, should be strengthened in the military.⁵⁰

However, those recommendations did not achieve their intended impact. Despite that input, Dr. Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, told a <u>Wall Street Journal</u> reporter that the adenovirus vaccine issue was "low on the radar screen." ⁵¹

In 1998, after an Adenovirus outbreak at Fort Jackson (the largest basic training site in the Army), the Armed Forces Epidemiological Board sent a second letter to the Pentagon about the urgency of making the vaccine available to new recruits and recommending it be given the highest priority. Key points of the Epidemiological Board's letter included:

- 1. Every reasonable effort must be made to insure adequate availability of oral adenovirus vaccine by:
 - a. Seeking an extension of expiration on the currently held adenovirus vaccine lots to spring of 1999.
 - b. Identifying a manufacturer to produce adequate supplies of adenovirus vaccine.
- 2. All recruits in training settings with known outbreaks of adenovirus illness should receive this vaccine on a year-round basis when vaccine is available.⁵²

After being briefed by infectious disease experts on 14 January 1998, Dr. Edward Martin, Acting Assistant Secretary of Defense for Health Affairs, requested that the Army Surgeon General conduct a cost benefit analysis of acquiring adenovirus vaccine.⁵³

The study showed that funding the vaccine would save money, as had been previously predicted. In August 1998, COL Rodney Michael, an Army infectious disease expert, advised Dr. Sue Bailey, the new Assistant Secretary of Defense for Health Affairs, that the adenovirus vaccine supplies were almost depleted. He estimated that it would cost \$15-\$25 million to find a new manufacturer for the vaccine. As reported in The Wall Street Journal, "Dr Bailey suggested that further research must be done to determine whether cheaper preventive measures, such as rigorous hand-washing and moving recruits' bunks farther apart, could match the vaccines' effectiveness." COL Michael stated that advocates of the vaccine were disheartened. Their feeling was that there was little evidence such measures were sufficient; vaccine experts felt they had failed and that their message was not understood. Dr. Sue Bailey stood by her decision, "since the healthcare budget was tight, if we do better prevention, rather than spend \$15 million for a vaccine for a virus that is not much worse than a bad cold and may not affect our ability to win a war, you may make a good dent. Either I was right, or no one else thought I was so wrong that they reversed it." "54"

EMERGENCE OF AN OLD NEMESIS

Since 1984 the U. S. military has administered live, enteric-coated adenovirus types 4 and 7 vaccines throughout the year and has successfully controlled adenovirus associated respiratory diseases among military recruits. In 1994, due to a logistical error, the adenovirus vaccines were not ordered for that year. This error resulted in production delays of the vaccines. From Summer of 1994 through Spring of 1995, administration of the adenovirus types 4 and 7 vaccines to basic trainees was temporarily suspended at Fort Jackson, South Carolina. When the adenovirus vaccination program resumed in March 1995, only new recruits received vaccines. About five to six weeks after resumption of the vaccination program, Company E, which had not received any adenovirus vaccinations, had a limited outbreak among the 220 male and female basic trainees. Most of the other trainees were immunized, so the infection did not spread to other companies. During the peak period of the epidemic over 70 soldiers per week were hospitalized at Moncrief Army Community Hospital; during this period the hospital's 45 bed ARD ward was also filled to capacity. There was a significant decline in new cases of acute respiratory disease and isolations of adenovirus type 4 shortly after the

restart of vaccination program in December 1995.⁵⁵ This outbreak of adenovirus indicates that basic trainees are susceptible to ARD due to adenovirus type 4.

In March 1997, Fort Jackson ceased administering adenovirus vaccines to trainees. During the latter half of 1997, there was a large outbreak of adenovirus type 4. After 8 weeks of training at Fort Jackson, most trainees go on to Advanced Individual Training (AIT) at various posts. That led to a major concern at Fort Gordon that adenovirus—associated ARD could spread to their AIT students. In May 1997, the Preventive Medicine staff at Fort Gordon and Fort Jackson implemented an intensive, laboratory surveillance program of trainees with febrile ARD. That surveillance showed that 90% of the 200 febrile ARD patients at Fort Jackson had type 4 adenovirus infections. Some Fort Gordon AIT soldiers who had recently completed basic training at Fort Jackson also had febrile ARD due to adenovirus type 4. The attack rate at Fort Jackson was 26.45 cases per 1000 basic trainees per month; at Fort Gordon, the attack rate was 7.5 cases per 1000 advanced individual trainees per month.⁵⁶

From October 1996 to June 1998 an adenovirus surveillance program was conducted at four military basic training sites on over 197,000 basic trainees. Of the 3413 throat cultures taken from trainees with febrile illness, 1814 (53.1%) were positive for adenovirus. The highest adenovirus culture yields (>90%) were September through November 1997, when there were two respiratory outbreaks at Fort Jackson and the Great Lakes Naval Training Center after cessation of the vaccine program. The epidemics affected thousands of trainees and severely stressed the local healthcare systems. Results confirmed that basic trainees are susceptible to large epidemics in the absence of adenovirus vaccines. If this is not corrected, morbidity among trainees may rival that prior to vaccine development. From summer of 1994 to Summer of 1999, some epidemics required hospitals to realign resources, convert barracks to infirmaries, open new infirmary wards, and cancel elective surgeries. Adenovirus type 4 was the major cause of febrile ARD at Fort Jackson, and emerged as a significant threat to safe and efficient basic training. This outbreak validated the Army's policy on vaccinating all recruits with adenovirus types 4 and 7 vaccines.

In April 2000, Fort Benning, Georgia experienced an adenovirus outbreak among its basic trainees. In just two days, Martin Army Community Hospital admitted 127 basic trainees for febrile upper respiratory illness, 112 from the same training company. Adenovirus type 4 was identified as the cause for the outbreak.⁵⁹

Because of the loss of the adenovirus vaccines there were concerns about a resurgence of pre vaccination levels of ARD outbreaks among basic trainees on military training posts. As a result the U.S. Army Center for Health Promotion and Preventive Medicine conducted a

retrospective nationwide seroprevalence survey to determine the current susceptibility of the trainee population to adenovirus types 4 and 7 and to assess the threat of the disease associated with the loss of the vaccines. Serologic data from 303 new recruits (samples taken from each state) in 1993 showed that basic trainees entering the military in the 1990s exhibit the same susceptibility to the threat of adenovirus types 4 and 7 as those recruits who entered the military prior to the adenovirus vaccination program in the military in the 1970s.⁶⁰

In April 2000, Dr Lemon, Chair of the Institute of Medicine Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military, reviewed the failure of Department of Defense to maintain a supply of adenovirus vaccine. On 6 November 2000, the Institute of Medicine reported to the Commanding General of the U.S. Army Medical Research and Materiel Command that "the Adenovirus vaccine was urgently needed to control the epidemic respiratory disease that has caused much morbidity among recruits in the past, and now once again threatens the health and even lives of military trainees; since acute pulmonary infection due to adenovirus is a nearly unique occupational risk of the military trainee, it is imperative that DOD take rapid and effective action to once more eliminate this preventable disease. The committee recommended that a much greater sense of urgency be placed on reacquiring an effective adenovirus vaccine; that a significantly larger and long term commitment be made to restore and maintain the ongoing availability of adenovirus vaccine; and that DOD not only evaluate the causes underlying this serious procurement system failure, but also make a clear commitment to the changes necessary to prevent similar breakdowns in the future."

Since the reported outbreaks in fall of 2000 the AFEB sent a third letter to top military health officials informing them of the need to re-start the program. Currently (Fall 2001) the U.S. Army Medical Material Development Activity in Fort Detrick is seeking statements of work to re-establish the production capability of Adenovirus Vaccines. The manufacturer will have to go through the full FDA new product approval process. The earliest projected date for a vaccine is three to four years down the road.

COST BENEFIT ANALYSIS

In 1966 the Army instituted an Adenovirus Surveillance Program to monitor acute respiratory disease in basic combat trainee populations and the efficacy of adenovirus vaccines in reducing ARD associated with adenovirus types 4 and 7. A 1973, a cost benefit analysis showed that the total cost of the vaccine program between 1966 and 1971 (development, purchase and administration) was \$4.83 million. On the other hand, cost for one recruit

admission to the hospital for ARD was \$279. Data showed that when types 4 and 7 vaccines were used together in 1971, the vaccination program averted approximately 26,979 admissions, saving the military an estimated \$7.53 million. This analysis demonstrated the cost-benefit derived from immunizing basic trainees.⁶²

After Wyeth closed its production facility, the Army conducted a Cost Effectiveness analysis in 1998 to assess the consequences of either changing the year-round Army Adenovirus Vaccination Program to seasonally targeted vaccine administration (only during high risk period), or abolishing the vaccination program. Analysis showed that if the adenoviral vaccination program were discontinued, approximately 12,370 recruits from a male recruit population of 76,171 would be hospitalized annually with ARD infections. This would cost the Army approximately \$26.4 million annually in medical and training related costs. If the Army implemented a seasonally targeted adenovirus vaccination program, approximately 7,800 episodes of ARD would be averted and save the Army about \$16.1 million. The study concluded that any adenovirus vaccination program would be cost effective and avert unnecessary hospitalizations. ⁶³

Army and Navy personnel, using 1997 naval recruit data, conducted a cost effectiveness analysis of re-acquiring and using adenovirus types 4 and 7 vaccines in naval recruits. Whereas the previous Army study analyzed only two policy options, the Navy analyzed three policy options: no vaccination; seasonal vaccination; and year-round vaccination. They used a population of 49,079 naval recruits. The study found that a policy of seasonal vaccination versus no vaccination would avert 4,015 cases and saves approximately \$2.8 million dollars per year. A year-round policy would prevent 4,555 cases and save approximately \$2.6 million per year. Both the Army and Navy analyses show that it would be cost effective to reacquire the adenovirus vaccines and to reinstitute the year-round policy. Spending \$12 million for a new vaccine production facility would pay for itself in 4 to 5 years. 64

IMPACT ON READINESS AND DEPLOYABILITY

Not funding Wyeth \$5 million to upgrade its vaccine facility resulted in the loss of the manufacturing capability for adenovirus vaccine. This created second and third order effects that pose a threat to U.S. military readiness. Adenovirus outbreaks can incapacitate commands, thereby halting the flow of new trainees into basic training. These outbreaks increase hospital days for basic trainees, and cause severe illnesses and even death. This leads to recycling of trainees, and increases costs for training. Adenoviruses now have the potential to cause outbreaks on warships; in the past, sailors in the close shipboard environment

would have been protected due to vaccinations received in training prior embarkation. During mobilization, depending on the number of personnel activated for basic training, 10% or more of our recruits could be hospitalized due to adenovirus; this could impede deployment plans.

IMPACT ON HEALTH CARE SYSTEM

The refusal of the Pentagon to fund the upgrade requested by Wyeth in 1984 has proven to be a very costly decision. In January 2000, the United States Army Medical Command Deputy Chief of Staff for Operations, Health Policy and Services, sent a memo to MEDCOM units informing them of the issue and prescribing guidelines for them to follow. He noted that since supplies of the adenovirus vaccines were low, adenovirus vaccine use at basic training sites in Fiscal Year 1996 had been restricted from September to March, instead of year-round. Since then there had been an increase in adenovirus infection rates among recruits. He recommended some non-vaccine acute respiratory disease interventions (NOVARDI) that may be effective:

- Hand Washing. The Navy initiated a "Stop Cough Program" in 1996 at Great
 Lakes. It consisted of mandatory hand-washing five times daily for recruits.
 Although there was a 45% reduction in out patient visits for respiratory illness there
 were no changes in hospitalization rates. This recommendation would be difficult
 to implement in a training environment.
- 2. Bunk Spacing. A minimum of 72 square feet between bunks for sleeping is easy to accomplish, but is difficult to maintain in a classroom environment.
- Cohorting, head to toe sleeping, and use of anti-microbial hand wipes. These
 methods have had limited success in the past but may delay the onset of ARD
 during the latter stages of training.⁶⁵

Studies show that out breaks of adenovirus ARD has stressed the health care system and increased operational cost. A cost analysis done in 1973 showed that the adenovirus vaccination program was cost effective and is the only reliable method to control adenovirus related ARD. Today we face the same issue of justifying the need for an adenovirus vaccination program. If the cost analysis study conducted in 1998 had been done four to six years earlier, Pentagon officials may have given higher priority to the adenovirus vaccination program and averted the current problem.⁶⁶

IMPACT OF PROCURING A NEW MANUFACTURER

Publicly available data does not reveal who decided to stop immunizing basic trainees with the adenovirus vaccines or to abolish the vaccination program. The record does document the reasons to delay the decision to fund the program. A short term "saving" resulted in higher long-term costs. Instead of \$5 million, DOD will now have to spend approximately \$25 million to get a manufacturer to produce this vaccine. As it prioritizes competing issues, the military must acknowledge that the adenovirus issue poses a severe risk to recruits and readiness. When the civilian DOD leadership designated this issue as a low priority, they failed to recognize the second- and third-order effects of their decision. It appears that there was a communication failure between the military and the civilian leadership which led the secretaries to make a decision that now adversely affects the military medical departments and basic trainees. To fulfill their vision of readiness, our senior military leaders must more effectively articulate our armed services' pressing needs. One is certainly the need to protect our trainees from adenoviral illnesses.

There are several issues that will impact on the timeline to obtain a new manufacturer for the adenovirus vaccine: vaccine efficacy, vaccine safety and risk of disease; the Food and Drug Administration approval process; and legal and licensure requirements. Resolving these issues may take years.

Efficacy: Vaccines are not 100% effective in preventing or limiting the impact of infection. Demonstration of vaccine effectiveness in protecting a particular group of individuals against exposure to a specific microorganism by a certain route is key in the regulatory approval process. These vaccines must have proven epidemiological studies before they are approved.

Safety: Vaccines used within DOD should be as safe as other vaccines. It is essential that human safety studies (both pre and post licensure) be conducted with the same rigor and objectivity as for vaccines used in civilian programs.

Risk and Benefit: The regulatory approval process looks at the balance between the risk of disease and the safety of the vaccine and the predicted benefit of the vaccine.

Legal issues: Many vaccine manufacturers are concerned about the potential to be sued by anyone who may have an adverse reaction to the vaccine

In 1996 Wyeth confirmed their decision to discontinue adenovirus vaccine production, but they agreed to transfer their technology to another manufacturer if the government would reimburse them. Greer Laboratories agreed to take over production, but withdrew from the

agreement when negotiations stalled in 1997; they wanted the government to fund \$10 to \$12 million up front cost.

Because adenovirus vaccine is used only by the military and has very little commercial value for civilian use, the government may have to fund the adenovirus vaccine research and development program.

There are several vaccines used by the military that have little commercial value. It may be in the best interest of DOD to build a full scale biologics production facility. This would entail approximately \$100 million in start up costs and about \$10 million annual operational costs. Under this model projected timeline to reacquire adenovirus vaccines is 2007.

CONCLUSION

Basic training places trainees in a unique situation, which puts them at great risk for adenovirus infection. DOD strategic leaders must do everything to protect these basic trainees against this well-documented and preventable infection. Studies have shown the adenovirus vaccine program to be cost effective; we must reinstate it as soon as possible. DOD must ensure long term commitment for funding for this adenovirus vaccine program. The loss of the adenovirus vaccine should serve as a warning against dependence on single manufacturer for critical military products.

Bioterrorism is no longer a remote threat. The history of the adenovirus vaccine program is but one example of why we must have more than one source for essential vaccines. Anthrax, smallpox, and other rising threats could have far greater effects on the United States.

To place the issue in the classic "ends-ways-means" relationship:

Ends

Combat ready soldiers available to the war-fighting commanders in chief.

Ways

Reduce preventable illnesses that drain scarce military resources.

Immunize military recruits against adenovirus type four and seven.

Means

Fund military research programs to develop and stockpile vaccines.

Fund civilian manufacturers' research and development costs for military-specific vaccines.

Word Count = 6,099

ENDNOTES

¹Franklin H. Top, Jr., "Control of Adenovirus Acute Respiratory Disease in U.S. Army Trainees," <u>The Yale Journal of Biology and Medicine</u>, no. 48 (1975): 191.

²lbid, 191.

³Colonel Edward Eitzen, Chief, Operational Medicine Division, U.S. Army Medical Research Institute of Infectious Diseases, interview by author, 14 August 2001, Frederick, Maryland.

⁴lbid.

⁵J. H. Dingle et al., "Epidemiology of acute respiratory disease in military recruits." <u>Am Rev Respir Dis</u>, no. 97 (1968): 6.

⁶Top, 186.

⁷lbid

⁸J.T. Grayston et al., "Adenoviruses. Their etiological role in acute respiratory disease in civilian adults," <u>Journal of Infectious Diseases</u>, no.103 (1958): 93.

⁹Top, 186.

¹⁰lbid.

¹¹Peter B. Collis et al., "Adenovirus Vaccines in Military Recruit Populations: A Cost benefit Analysis," <u>The Journal of Infectious Diseases</u> 12, no.128 (1973): 745.

¹²Wallace P. Rowe et al., "Isolation of a Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in tissue Culture," <u>Proc Soc Exp Biol Med</u>, no. 84 (1954): 573.

¹³Ibid. 571.

¹⁴M. R. Hilleman et al., "Recovery of new Agent from patients with Acute Respiratory Illness," <u>Proc Soc Exp Biol Med</u>, no. 85 (1954): 183-188.

¹⁵Ibid, 188.

¹⁶J. F. Enders et al., "Adenovirus: Group name Proposed for New Respiratory-Tract Viruses," <u>Science</u>, no.124 (1956): 119.

¹⁷Dingle, 6.

¹⁸B. A. Dudding et al., "Acute Respiratory Disease in military trainees. The Adenovirus Surveillance Program 1966-1971," <u>American Journal of Epidemiology</u>, no. 97 (1973): 187-198.

¹⁹B. A. Dudding et al., "Fatal Pneumonia associated with adenovirus type 7 in three military recruits," New England Journal of Medicine, no. 286 (1972): 1289.

```
<sup>20</sup>Ibid, 1291.
```

²⁴Charlotte A. Gaydos, "Adenovirus Vaccines in the U.S. Military," <u>Military Medicine</u> 6, no.160 (1995): 301-304.

²⁵Department of the Army, <u>Conterminous United States Basic Facilities and Space</u>
<u>Allowances for Construction at Installations in Event of Emergency</u>, Army Regulation 415-50 (Washington, D.C.: U.S. Department of the Army, August 1964).

²⁶lbid.

²⁷M. R. Hilleman et al., "Prevention of Acute Respiratory Illness in Recruits by Adenovirus (RI-APC-ARD) Vaccine," <u>Pro Soc Exp Biol Med</u>, no. 92 (1956): 377.

²⁸Ibid, 379.

²⁹Ibid. 380.

30 Ibid.

³¹Ibid, 382.

³²Top, 187.

³³R. B. Couch et al., "Immunization with types 4 and 7 adenovirus by selective infection of the intestinal tract," <u>American Review of Repiratory Diseases</u>, no. 88 (Suppl) (1963): 394.

³⁴R. M. Chanock et al., "Immunization by selective infection with type 4 adenovirus grown in human diploid culture. 1. Safety and lack of oncogenicity and tests for potency in volunteers," <u>JAMA</u>, no. 195 (1966): 445.

³⁵Dudding, 196-197.

³⁶Collis, 746.

³⁷Dudding, 197.

³⁸Top, 191.

²¹Top, 185.

²²Ibid, 186.

²³lbid.

- ⁴⁰Gregory C. Gray et al., "Adult Adenovirus Infections: Loss of Orphaned Vaccines Precipitates Military Respiratory Disease Epidemics," <u>Clinical Infectious Diseases</u>, no. 31 (2000): 665.
- ⁴¹Department of Health and Human Services, <u>Adult Immunization Recommendations of the Immunization Practices Advisory Committee (ACIP)</u>, (Atlanta. GA.: Center for Disease Control, 1984).
- ⁴²Department of Defense Instruction, <u>Immunization Requirements</u>, Department of Defense Instruction Number 6205.2 (Washington D.C.: Department of Defense, 9 October 1986).
- ⁴³Department of the Army, <u>Immunization and Chemoprophylaxis</u>, Army Regulation 40-562 (Washington D.C.: U.S. Department of the Army, 1 Nov 1995).
- ⁴⁴James B. Peake, <u>A statement on the Posture of Health Care in the United States Army,</u> <u>Fiscal Year 2001</u>, Posture Statement presented to the 107th Cong., 1st sess. (Washington, D.C.: U.S. Department of the Army, 2001).
- ⁴⁵Sarah Lueck, "Outbreak; A common Virus, A military Recruit And a Mysterious Death After Two decades, The Army Pulls the Plug on Vaccine; Boot-Camp Bug is back—Chorus of Coughs in barracks," <u>The Wall Street Journal</u>, (13 July 2001): 3 [database on-line]; available from UMI ProQuest, Bell & Howell; accessed 6 August 2001.
- ⁴⁶Deputy Chief of Staff for Operations, Health Policy and Services, "Adenovirus Disease Control," memorandum for Commanders, MEDCOM Major Subordinate Commands, Fort Sam Houston, Texas, 21 Jan 2000.
 - ⁴⁷J. C. Gaydos, Loss of Adenovirus Vaccine, Information Paper 24 April 1996.
- ⁴⁸Mills K. McNeil et al., "Large persistent Epidemic of Adenovirus Type 4-Associated Acute Respiratory Disease in U.S. Army Trainees," <u>Emerging Infectious Diseases</u> 5, no. 6 (Nov-Dec 2000): 1-6.
- ⁴⁹Anonymous, "Two Fatal Cases of Adenovirus-Related Illness in Previously Healthy Young Adults-Illinois, 2000," <u>Morbidity and Mortality Weekly Report</u> (6 July 2001): 1-3 [database online]; available from UMI ProQuest, Bell & Howell; accessed 6 August 2001.
- ⁵⁰President AFEB, "Recommendations Concerning Adenovirus Vaccine Program," memorandum for The Assistant Secretary of Defense (Health Affairs), The Surgeon General of the Army, Air Force and Navy, Falls Church, VA, 28 February 1995.

³⁹Gaydos, 302.

⁵¹Lueck, 4.

⁵²President AFEB, "Recommendations Concerning Adenovirus Vaccine Program," memorandum for The Assistant Secretary of Defense (Health Affairs), The Surgeon General of the Army, Air Force and Navy, Falls Church, VA, 9 January 1998.

⁵³Acting Assistant Secretary of Defense Edward D. Martin, "Request for Cost Benefit Analyses of Acquiring Adenovirus Vaccine," memorandum for Surgeon Generals of the Army, Navy and Air Force, Washington, D. C., 14 Jan 1998.

⁵⁴Lueck, 4.

⁵⁵Evelyn M. Barraza et al., "Reemergence of Adenovirus type 4 Acute Respiratory Disease in Military Trainees; Report of an Outbreak during a lapse in Vaccination," <u>The Journal of Infectious Diseases</u>, no. 179 (1999): 1531-1533.

⁵⁶Mills K. McNeil et al., "Epidemic Spread of Adenovirus Type 4-Associated Acute Respiratory Disease between U.S. Army Installations," <u>Emerging Infectious Diseases</u> 6, no. 4 (Jul-Aug 2000): 1.

⁵⁷Gray, 663.

58 Ibid.

⁵⁹Army Center for Health Promotion and Preventive Medicine, "<u>Adenovirus type 4 Outbreak among basic Trainees at Ft. Benning, Georgia, April-May 2000</u>." Medical Surveillance Monthly Report (Aberdeen Proving Ground, MD., July 2000)6: 1-8.

⁶⁰Sharon L. Ludwig et al., "Prevalence of Antibodies to Adenovirus serotypes 4 and 7 among U.S. Army Trainees: Results of a Retrospective Nationwide Seroprevalence Survey," <u>The Journal of Infectious Disease</u>, no. 178 (1998): 176-178.

⁶¹Stanley Lemon, Chair, for Institute of Medicine, "Urgent Attention Needed to Restore Adenovirus Vaccine Availability." memorandum for Commanding General U.S. Army Medical Research and Materiel Command, Fort Detrick MD, 6 November 2000.

⁶²Collis, 746.

⁶³Rene M. Howell et al., "Prevention of Adenoviral Acute Respiratory Disease in Army Recruits: Cost Effectiveness of a Military Vaccination program." <u>American Journal of Preventive Medicine</u>, no. 14 (1998): 168.

⁶⁴Randall N. Hyer et al., "Cost Effectiveness Analysis of Reacquiring and using Adenovirus Types 4 and 7 Vaccines in Naval Recruits," <u>American Society of Tropical Medicine and Hygiene</u> 5, no. 65 (2000): 613.

⁶⁵Deputy Chief of Staff for Operations, Health Policy and Services, "Adenovirus Disease Control," memorandum for Commanders, MEDCOM Major Subordinate Commanders, Fort Sam Houston, Texas, 21 January 2000.

⁶⁶Howell, 168.

BIBLIOGRAPHY

- Anonymous. "Two Fatal Cases of Adenovirus-Related Illness in Previously Healthy Young Adults-Illinois, 2000." Morbidity and Mortality Weekly Report, (6 July 2001): 1-3. Database on-line. Available from UMI ProQuest, Bell & Howell. Accessed 6 August 2001.
- Barraza, Evelyn M., Sharon L. Ludwig, JoeL C. Gaydos, and John F. Brundage. "Reemergence of Adenovirus type 4 Acute Respiratory Disease in Military Trainees; Report of an Outbreak during a lapse in Vaccination." <u>The Journal of Infectious Disease</u>, no. 179 (1999): 1531-1533.
- Chanock, R. M., W. Ludwig, Robert J. Huebner, Thomas R. Cate, and Liang-Weiu Chu. "Immunization by selective infection with type 4 adenovirus grown in human diploid culture. 1. Safety and lack of oncogenicity and tests for potency in volunteers." <u>JAMA</u>, no. 195 (1966): 445-452.
- Collis, Peter B., Burton A. Dudding, Philip E. Winter, Philip K. Russell, and Edward L Buesher. "Adenovirus Vaccines in Military Recruit Populations: A Cost benefit Analysis." <u>The Journal of Infectious Disease</u> 12, no.128 (1973): 745-751.
- Colonel Edward Eitzen, Chief, Operational Medicine Division, U.S. Army Medical Research Institute of Infectious Diseases, interview by author, 14 August 2001, Frederick, Maryland.
- Couch, R. B., R. M. Chanock, T. R. Cate, D. J. Lang, V. Knight, and R. J. Huebner, .

 "Immunization with types 4 and 7 adenovirus by selective infection of the intestinal tract."

 <u>American Review of Repiratory Diseases</u>, no. 88 (Suppl) (1963): 394-403.
- Deputy Chief of Staff for Operations, Health Policy and Services. "Adenovirus Disease Control." Memorandum for Commanders, MEDCOM, Major Subordinate Commanders. Fort Sam Houston, Texas, 21 January 2000.
- Dingle, J. H., and A. D. Langmuir. "Epidemiology of acute respiratory disease in military recruits." Am Rev Respir Dis, no. 97 (1968): 6-13.
- Dudding, Burton A., Franklin H. Top Jr., Robert M. Scott, Philip K. Russell, and Edward L. Buesher. "An Analysis of Hospitalizations for Acute Respiratory Disease in Recruits Immunized with Adenovirus Type 4 and Type 7 Vaccines." <u>American Journal of Epidemiology</u>, no. 95 (1972): 140-147.
- Dudding, Burton A., Franklin H. Top Jr., Philip Winter, Edward L. Buescher, Thomas H. lamson and, Albert Leibovitz. "Acute Respiratory Disease in military trainees. The Adenovirus Surveillance Program 1966-1971." <u>American Journal of Epidemiology</u>, no. 97 (1973): 187-98.
- Dudding, Burton A., Stanley C. Wagner, Jack A. Zeller, John T. Gmelich, George R. French, and Franklin H. Top. "Fatal Pneumonia associated with adenovirus type 7 in three military recruits." New England Journal of Medicine, no. 286 (1972): 1289-1292.
- Enders, Joseph A., John A. Bell, John H. Dingle, Thomas Francis Jr., and Robert H. Huebner. "Adenovirus: Group name Proposed for New Respiratory-Tract Viruses." <u>Science</u>, no.124 (1956): 119-120.

- Foy, Hjordis M. "Adenoviruses." In <u>Viral Infections of Humans</u>, 4th ed. Alfred S. Evans and Richard A., Kaslow, 119-138. New York: Plenium, 1997.
- Gaydos, Charlotte A., " Adenovirus Vaccines in the U.S. Military." Military Medicine 6, no.160 (1995): 301-304.
- Gaydos, J. C., Loss of Adenovirus Vaccine. Information Paper, 24 April 1996.
- Gray, Gregory C., Pulak R. Goswami, Marietta D. Malasig, Anthony W. Hawksworth, David H. Trump, Margaret A. Ryan, and David P. Schmurr. "Adult Adenovirus Infections: Loss of Orphaned Vaccines Precipitates Military Respiratory Disease Epidemics." Clinical Infectious Diseases, no. 31 (2000): 663-670.
- Grayston, J.T., J. C. Lashof, C. G. Loosli, and P. B. Johnston. "Adenoviruses. Their etiological role in acute respiratory disease in civilian adults." <u>Journal of Infectious Diseases</u>, no.103 (1958): 93-101.
- Hilleman, M. R., and Jacqueline H. Werner. "Recovery of new Agent from patients with Acute Respiratory Illness." <u>Proc Soc Exp Biol Med</u>, no. 85 (1954): 183-188.
- Hilleman, M. R., R. L. Stallones, R. L. Gauld, M. S. Warfield, and S. A. Anderson. "Prevention of Acute Respiratory Illness in Recruits by Adenovirus (RI-APC-ARD) Vaccine." Proc Soc Exp Biol Med, no. 92 (1956): 377-383.
- Howell, Rene M., Roberto N. Nang, Charlotte A. Gaydos, and Joel C. Gaydos. "Prevention of Adenoviral Acute Respiratory Disease in Army Recruits: Cost –Effectiveness of a Military Vaccination program." Medicine, no. 14 (1998): 168-175.
- Hyer, Randall N., Rene M. Howell, Margaret K. Ryan, and Joel C. Gaydos. "Cost Effectiveness Analysis of Reacquiring and using Adenovirus Types 4 and 7 Vaccines in Naval Recruits." American Society of Tropical Medicine and Hygiene 5, no. 65 (2000): 613-618.
- Lemon, Stanley, "Urgent Attention Needed to Restore Adenovirus Vaccine Availability." Institute of Medicine Memorandum for Commanding General U.S. Army Medical Research and materiel Command, Fort Detrick MD., 6 November 2000.
- Ludwig, Sharon L., John F. Brundage, Patrick W. Kelley, Roberto Nang, Cynthia Towle, David P. Schmurr, Leta Crawford-Miksza, and Joel C. Gaydos. "Prevalence of Antibodies to Adenovirus serotypes 4 and 7 among U.S. Army Trainees: Results of a Retrospective Nationwide Seroprevalence Survey." The Journal of Infectious Disease, no. 178 (1998): 176-178.
- Lueck, Sarah. "Outbreak; A common Virus, A military Recruit And a Mysterious Death After Two decades, The Army Pulls the Plug on Vaccine; Boot-Camp Bug is back-Chorus of Coughs in barracks." The Wall Street Journal, (13 July 2001): 1-5. Database on-line. Available from UMI ProQuest, Bell & Howell. Accessed 6 August 2001.
- Martin, Edward D., Acting Assistant Secretary of Defense. "Request for Cost Benefit Analyses of Acquiring Adenovirus Vaccine." Memorandum for Surgeon Generals of the Army, Navy and Air Force. Washington, D. C., 14 January 1998.

- McNeil, Mills K., Rose M., Hendrix, Jane L. Linder, Ridgely, F. Benton, Susan C. Monteith, Margaret A. Tuchscherer, Gregory C. Gray, and Joel C. Gaydos. "Large persistent Epidemic of Adenovirus Type 4-Associated Acute Respiratory Disease in U.S. Army Trainees." Emerging Infectious Diseases 5, no. 6 (Nov-Dec 2000): 1-6.
- McNeil, Mills K., Ridgely F. Benton, Susan C. Monteith, Margaret A. Tushscherer, and Joel C. Gaydos. "Epidemic Spread of Adenovirus Type 4-Associated Acute Respiratory Disease between U.S. Army Installations," <u>Emerging Infectious Diseases</u> 6, no. 4 (Jul-Aug 2000): 1-5.
- Peake, James B., <u>A Statement on the Posture of Health Care in the United States Army, Fiscal Year 2001</u>. Posture Statement presented to the 107th Cong., 1st sess. Washington, D.C.: U.S. Department of the Army, 2001.
- Plotkin, Stanley A., and Edward A. Mortimer. <u>Vaccines</u>, 2nd ed. Philadelphia: W.B. Saunders, 1994.
- President Armed Forces Epidemiological Board. "Recommendations Concerning Adenovirus Vaccine Program." Memorandum for The Assistant Secretary of Defense (Health Affairs), The Surgeon General of the Army, Air Force and Navy. 28 February 1995.
- President Armed Forces Epidemiological Board. "Recommendations Concerning Adenovirus Vaccine Program." Memorandum for The Assistant Secretary of Defense (Health Affairs), The Surgeon General of the Army, Air Force and Navy. 9 January 1998.
- Rowe, Wallace P., Robert J. Huebner, Loretta K. Gilmore, Robert H. Parrott, and Thomas G. Ward. "Isolation of a Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in tissue Culture." <u>Proc Soc Exp Biol Med</u>, no. 84 (1954): 570-573.
- Top, Franklin H. Jr., "Control of Adenovirus Acute Respiratory Disease in U.S. Army Trainees," The Yale Journal of Biology and Medicine, no. 48 (1975): 185-195.
- Top, Franklin H. Jr., Burton A. Dudding, Philip K. Russell, and Edward L. Buescher. "Control of Respiratory Disease in Recruits with Types 4 and 7 Adenovirus Vaccines." American Journal of Epidemiology, no.94 (1971): 142-146.
- U.S. Army Center for Health Promotion and Preventive Medicine. Adenovirus type 4 Outbreak among basic Trainees at Ft. Benning, Georgia, April-May 2000. Medical Surveillance Monthly Report. Aberdeen proving Ground, MD: July 2000: 6, 1-8.
- U. S. Continental Congress. Regulations for the order and discipline of the Troops of the United States, part 1, 29 March 1779.
- U.S. Department of the Army. <u>Immunization and Chemoprophylaxis.</u> Army Regulation 40-562. Washington D.C.: U.S. Department of the Army, 1 Nov 1995.
- U. S. Department of the Army. <u>Conterminous United States Basic Facilities and Space</u>
 <u>Allowances For Construction at Installations in Event of Emergency</u>. Army Regulation 415-50. Washington D.C.: U.S. Department of the Army, August 1964.

- U.S. Department of Defense. <u>Immunization Requirements</u>, Department of Defense Instruction Number 6205.2. Washington D.C.: Department of Defense, 9 October 1986.
- U.S. Department of Health and Human Services: "Adult Immunization Recommendations of the Immunization Practices Advisory Committee (ACIP)." Atlanta, GA.: Center for Disease Control, 1984.